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https://doi.org/10.1038/s41587-019-0045-y

Wearable biosensors for healthcare monitoring

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Wearable biosensors are garnering substantial interest due to their potential to provide continuous, real-time physiological information via dynamic, noninvasive measurements of biochemical markers in biofluids, such as sweat, tears, saliva and interstitial fluid. Recent developments have focused on electrochemical and optical biosensors, together with advances in the noninvasive monitoring of biomarkers including metabolites, bacteria and hormones. A combination of multiplexed biosensing, microfluidic sampling and transport systems have been integrated, miniaturized and combined with flexible materials for improved wearability and ease of operation. Although wearable biosensors hold promise, a better understanding of the correlations between analyte concentrations in the blood and noninvasive biofluids is needed to improve reliability. An expanded set of on-body bioaffinity assays and more sensing strategies are needed to make more biomarkers accessible to monitoring. Large-cohort validation studies of wearable biosensor performance will be needed to underpin clinical acceptance. Accurate and reliable real-time sensing of physiological information using wearable biosensor technologies would have a broad impact on our daily lives.

Wearable sensors have received much attention since the arrival of smartphones and other mobile devices, owing to their ability to provide useful insights into the performance and health of individuals[1–6]. Early efforts in this area focused on physical sensors that monitored mobility and vital signs, such as steps, calories burned or heart rate. The face of wearable devices has changed rapidly in recent years, with researchers branching out from tracking physical exercise activity to focus on tackling major challenges in healthcare applications, such as the management of diabetes or remote monitoring of the elderly. To accomplish these goals, researchers have devoted substantial efforts to the development of wearable biosensors, which are defined as sensing devices that incorporate a biological recognition element into the sensor operation (for example, enzyme, antibody, cell receptor or organelle). The potential utility of wearable biosensors is evident from the rapidly increasing rate of newly reported proof-of-concept studies. Although several of these platforms are under clinical evaluation, successful translation to the commercial market has been lacking. Significant endeavors are underway toward the commercialization of noninvasive biosensors. However, these products still require further large-scale validation studies, the necessary device regulatory approvals and final marketing paths. Driven by the promise of the huge glucose sensing market, this commercial activity focuses largely on minimally invasive glucose monitoring devices, as illustrated in the representative examples given in Table 1.

A typical biosensor contains two basic functional units: a 'bioreceptor' (for example, enzyme, antibody or DNA) responsible for selective recognition of the target analyte and a physico-chemical transducer (for example, electrochemical, optical or mechanical) that translates this biorecognition event into a useful signal (Fig. 1a). Such devices were initially developed for in vitro measurements in controlled (laboratory or point-of-care) settings or for single-use home testing (for example, blood glucose test strips). A brief history of biosensing technologies preceding current wearable biosensors[7–38] is provided in Fig. 1b. These past advances have paved the way to modern wearable biosensors for noninvasive biomonitoring applications as an alternative to blood monitoring biomedical devices in connection to wide range of healthcare applications.

Biosensors hold considerable promise for wearable applications due to their high specificity, speed, portability, low cost and low power requirements. Indeed, innovative biosensor platforms for noninvasive chemical analysis of biofluids, such as sweat, tears, saliva or interstitial fluid (ISF), have already been widely applied to a variety of head-to-toe application sites, targeting an array of important analytes in proof-of-concept demonstrations (Fig. 2)[32–36,39–44]. Sweat, tears, saliva and ISF have been targeted as they can be sampled in a noninvasive manner, meaning that they can be readily accessed without disrupting the outermost protecting layers of the body's skin (the stratum corneum) and without contacting blood. As such, noninvasive sensing methods pose minimal risk of harm or infection and are generally more user friendly.

The wide acceptance of such wearable biosensor technology requires a deep understanding of the biochemical composition of bodily fluids, such as sweat or tears, and its relation to blood chemistry. Wearable monitoring platforms can lend insights into dynamic biochemical processes in these biofluids by enabling continuous, real-time monitoring of biomarkers that can be related to a wearer's health and performance. Such real-time monitoring can provide information on wellness and health, enhance the management of chronic diseases and alert the user or medical professionals of abnormal or unforeseen situations. Wearable biosensors can obviate painful and risky blood sampling procedures and can be readily blended with a wearer's daily routine. To accomplish this capability, the biosensing platform must provide direct contact with the sampled biofluids without inducing discomfort to the wearer. Such body compliance can be achieved through use of advanced materials and smart designs that provide the necessary flexibility and stretchability[45–48]. Continuous multidisciplinary development of new biosensing technologies (and corresponding new materials and energy sources) has led to numerous proof-of concept demonstrations and has driven growing efforts toward the commercialization activity of wearable sensors.

The attractive capabilities of modern wearable chemical and physical sensors and related research advances have been highlighted in several recent reviews[2,29,48–53]. Unlike physical or chemical wearable sensors, the wearable biosensors reviewed here rely on highly specific bioreceptors capable of recognizing target analytes in complex samples at physiologically relevant concentrations. Despite rapid progress in wearable biosensor technology over the past 5 years, we are only at the beginning of understanding how wearable biosensor technologies can improve health and performance.

In the following Review, we provide an overview of the key advances in wearable biosensors from the past 2 years and discuss their potential as alternatives to invasive biomedical devices and

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Table 1 | Selected examples of commercial noninvasive or minimally invasive biosensors

Product, company	Analyte, sample	Wearable platform	Monitoring mechanism	Current stage	Website
Smart contact lens, Google and Novartis	Glucose in tears	Contact lens	Electrochemistry	Last update in 2018; this project is now on hold	https://verily.com/projects/sensors/smart-lens-program/
GlucoWatch, Cygnus Inc.	Glucose in ISF	Watch type	Electrochemistry	FDA approved, but retracted from market	No longer available
BioMKR, Prediktor Medical	Blood glucose	Wrist strap similar to a smart watch	Near infrared spectroscopy, bioimpedance	Under clinical testing for approval and market launch in Europe	https://www.prediktormedical.com/
GlucoWise, MediWise	Blood glucose	Finger clip	Radio frequency	Under development, running clinical trials with healthy volunteers	http://www.glucowise.com/
Freestyle Libre, Abbott	Glucose in ISF	Patch	Electrochemistry	FDA approved in US in July 2018	https://www.freestylelibre.us/
Dexcom G6 CGM, Dexcom	Glucose in ISF	Patch	Electrochemistry	FDA approved	https://www.dexcom.com/
GlucoTrack, Integrity Applications	Blood glucose	Finger clip	Ultrasonic, electromagnetic, thermal waves	Type 2 diabetes, approved in Europe	http://www.glucotrack.com/
Eversense, Senseonics	ISF glucose	Subcutaneous small stick implant	Fluorescence	Recently received FDA approval	https://www.eversensediabetes.com/
NovioSense tear glucose sensor, NovioSense	Tear glucose	Small stick (spiral type) placed under the lower eyelid	Electrochemistry	Tested in animals and human subjects	http://noviosense.com/

to gold-standard blood assays. In particular, we discuss how the fundamental principles of biosensor systems can be adapted to the design of reliable wearable biosensors, we highlight key challenges in operating biosensors in specific noninvasive biofluids and the physiological relevance of monitoring key biomarkers in these fluids, and finally, we provide an overview of the overall importance and future prospects of wearable biosensing devices for the biomedical field. We critically review pioneering studies that greatly influenced the field of wearable biosensing and address future challenges to overcome. Most of the studies discussed here involve biosensing devices based on electrochemical signal transduction, along with some based on optical sensing devices, as these transduction mechanisms have been the most commonly reported on over the past several years. We emphasize systems aiming at practical healthcare applications with promise for clinical translation in the near future.

The commercialization of wearable bioanalyte sensors is substantially more challenging than that of activity-tracking counterparts or common lab-based biosensors because such devices must be capable not only of continuous on-body biochemical sensing but also of reliable measurement of a biorecognition element (or elements) that is highly specific yet fragile. Robust, reliable measurement also must overcome such challenges as gradual surface biofouling at the body–sensor interface, inefficient transport of sample over the sensor, limited stability of many bioreceptors, the complexity of multistep bioaffinity assays and related receptor regeneration, and issues posed by calibration for on-body biosensors. In each section below, we discuss specific challenges related to each particular system and biofluid. Finally, we discuss future research and commercialization prospects, highlight existing bottlenecks and present our perspective on the prospects for this exciting research area.

Epidermal wearable biosensors

As the epidermis covers most of our body, skin-worn conformal devices have received the greatest recent attention among the various types of wearable biosensors. Epidermal biosensors can facilitate real-time analysis of biomarkers in epidermal biofluids (sweat and ISF), with some systems exhibiting continuous monitoring capabilities toward a variety of biomedical and fitness applications. These devices rely on sweat or ISF sampling at the skin surface, along with transport of these biofluids over the biosensor surface. Such skin-worn biosensors commonly rely on different transduction modes (for example, optical, electrochemical and mechanical) in combination with biocatalytic and ion-recognition receptors. Further integration with data processing and transmission components are necessary for a fully wearable platform. The majority of recent reports, however, have focused on electrochemical and colorimetric transduction methodologies. Major progress has been made toward a variety of skin-worn platforms offering the capability to readily sample epidermal biofluids with wearer comfort[3,34,35,40,42,50,54–63]. Such devices have been realized through direct transfer of sensors onto the skin (using E-skin or printed temporary tattoos), by sensor incorporation into wristbands and patches, or by embedding sensors directly into textiles to ensure tight contact with the skin while allowing the sensors to endure the mechanical stresses encountered during body movements.

Secretion and composition of epidermal biofluids (sweat, ISF). Sweat is the most readily obtainable biofluid for chemical sensing applications since sweat glands are distributed across the entire body, with more than 100 glands/cm^2 of skin. This physiology provides the most viable sampling sites and surface area outside the body. However, sweat must be excreted to the outer skin surface to be analyzed. Such sweat generation can be accomplished through exercise activity, thermal heating, stress or iontophoretic stimulation. Generally, sweat contains metabolites (for example, lactate, glucose, urea, ethanol or cortisol) along with electrolytes (for example, sodium, potassium, chloride or ammonium), trace elements (for example, zinc or copper) and small amounts of large molecules (for example, proteins, nucleic acids, neuropeptides or cytokines)[64]. These biomarkers make in situ sweat analysis of considerable

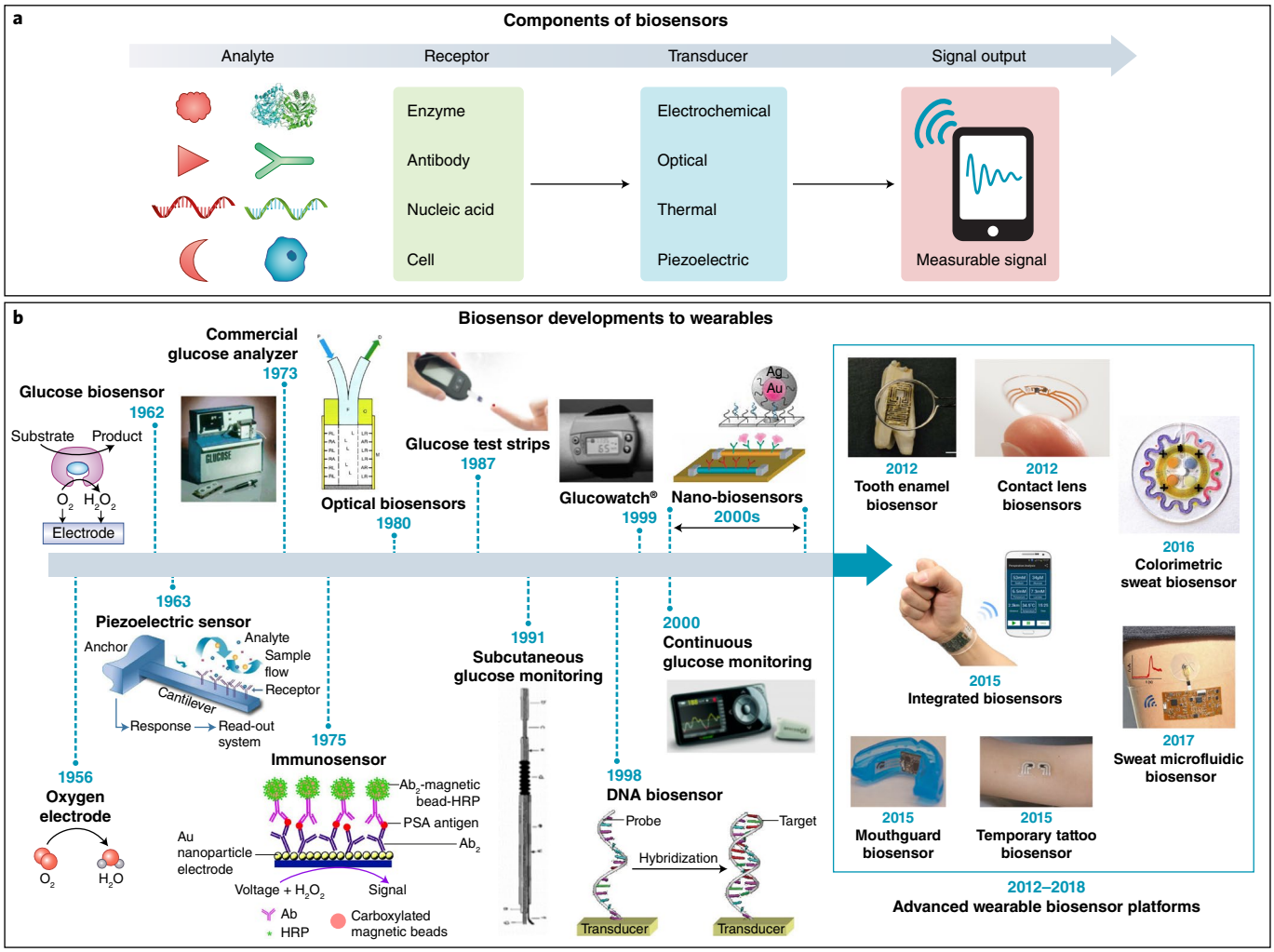

Fig. 1 | Biosensor components and the path of biosensor development for wearables. a, Schematic representation of biosensor operation principles: target analyte detection by the corresponding receptor molecule followed by signal transduction method and output. **b**, The concept of enzyme electrodes was proposed by Clark and Lyons[7] in 1962. Their device relied on entrapment of the enzyme GOx over an amperometric oxygen electrode that monitored the oxygen consumed by the biocatalytic reaction. Clark's electrochemical biosensor technology was transferred to the Yellow Spring Instrument (YSI) Company, which launched the first dedicated blood glucose analyzer (YSI Model 23 Analyzer) in 1975. Biosensors gained popularity during the 1980s, reflecting the growing emphasis on biotech. New biosensor transduction principles were introduced during this decade, including fiber-optic and mass-sensitive (piezoelectric) devices[8–14]. Considerable efforts during the 1980s led also to the introduction of commercial self-testing blood glucose strips that used mediator-based enzyme electrodes[15,16]. Subsequent activity during the 1990s resulted in subcutaneously implantable needle-type electrodes for real-time in vivo glucose monitoring[17]. These subcutaneously implantable glucose sensors moved in the early 2000s to commercial continuous glucose monitors that track in real-time the glucose level in the ISF, along with diabetes-relevant trends and patterns[18,19]. The emergence of nanotechnology in the late 1990s has led to variety of nanomaterial-based biosensors exploiting the attractive properties of different nanomaterials, such as silicon nanowires and gold nanoparticles, for label-free or amplified biosensing, respectively[20,21]. The specific base-pair recognition of DNA sequences led to the development of different DNA biosensors in the late 1990s[22–24]. Such nucleic acid sensors are playing a growing role in genomic sequence analysis. These advances in biosensor technology over the past five decades paved the way to modern wearable biosensors, discussed in this article. (Glucose biosensor adapted from J.W. et al.[25]. Piezoelectric sensor adapted from ref. [26]. Commercial glucose analyzer adapted from ref. [27]. Immunosensor adapted from ref. [28]. Optical biosensor adapted from ref. [10]. Glucose test strips adapted from ref. [29]. Subcutaneous glucose monitoring adapted from ref. [17]. GlucoWatch adapted from ref. [30]. DNA biosensor adapted from ref. [24]. Continuous glucose monitoring adapted from ref. [31]. Top nanobiosensors adapted from ref. [21]. Bottom nanobiosensors adapted from ref. [20]. Tooth enamel biosensor adapted from ref. [32]. Contact lens sensors adapted from ref. [33]. Colorimetric sweat biosensor adapted from ref. [34]. Integrated biosensors adapted from ref. [35]. Mouthguard biosensor adapted from J.K., J.W et al.[36]. Temporary tattoo biosensor adapted from J.W. and colleagues[37]. Sweat microfluidic sensor adapted from J.K., A.S.C., J.W. et al.[38]).

interest for noninvasive monitoring of physiological health status (for example, hydration or physical stress) and for disease diagnosis and management (for example, in such conditions as cystic fibrosis or diabetes). Noninvasive monitoring at the epidermis eliminates issues related to blood sampling while maintaining the protective stratum corneum skin layer intact. Yet additional research is needed for determining and validating the clinical value of sweat as a diagnostic biofluid. Target sweat analytes are each transported to the sweat from surrounding capillaries with unique partitioning profiles, making reliable correlation to concurrent blood concentrations difficult. Analytes can reach the sweat by passive (i.e., diffusion) or active mechanisms and can be also generated within the sweat duct itself. Although variations in sweat rate can be monitored using multiplexed analysis (i.e., simultaneous monitoring of

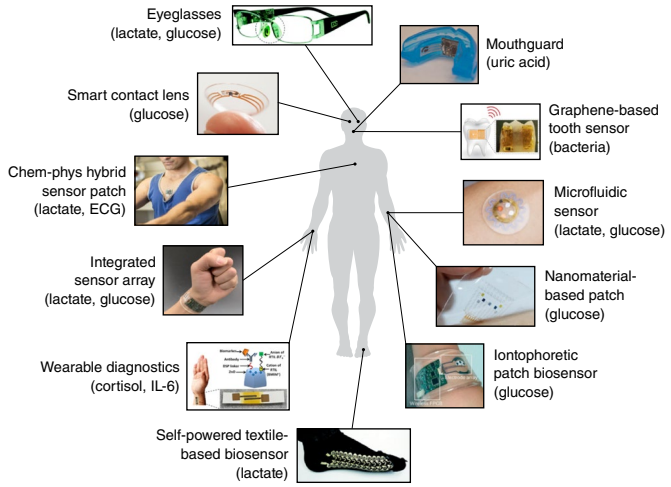

Fig. 2 | Representative examples of wearable biosensors. Clockwise from top: eyeglasses-based wireless electrolyte and metabolite sweat sensor (adapted from J.W. et al.[39]). Wearable mouthguard-based biosensor for salivary uric acid (adapted from J.K., J.W. et al.[36]). Graphene-based wireless bacteria sensor applied on tooth enamel (adapted from ref. [32]). Wearable microfluidic sweat sampling device for colorimetric sensing of sweat (adapted from ref. [34]). Graphene-based sweat sensor with thermoresponsive microneedles for diabetes monitoring and therapy (adapted from ref. [40]). Integrated wearable sensor arrays for multiplexed sweat extraction and analysis (adapted from ref. [41]). Stretchable self-powered sweat biosensors on a textile (adapted from J.W. et al.[42]). Sweat-based wearable diagnostics biosensors using room-temperature ionic liquids (adapted from ref. [43]). Integrated multiplexed wearable sensor arrays for in situ perspiration analysis (adapted from ref. [35]). Wearable chemical-electrophysiological (lactate/electrocardiogram) hybrid biosensor for real-time health and fitness monitoring (adapted from J.W. et al.[44]). Smart contact-lens biosensing platform for glucose monitoring in tears (adapted from ref. [33]).

analytes with concentration profiles that are independent of sweat rate) or skin impedance measurements, the degree of analyte dilution during sweat excretion is affected by the relationship between sweat rate and analyte partitioning rate[64]. Deeper understandings of sweat chemistry and transport, along with advances in sweat sampling and detection technologies, should accelerate sweat-based diagnostic opportunities.

Alternatively, epidermal biosensing systems have targeted measurements of analyte concentrations in ISF. Within viable skin tissue, skin cells are surrounded by ISF, which provides nutrients that diffuse directly from the capillary endothelium. This function, along with the associated ISF composition, leads to reliable correlations between the blood and ISF concentrations of many analytes, including electrolytes (for example, sodium, phosphate, magnesium, potassium or calcium), metabolites (for example, glucose, alcohol, lactate or cortisol) and proteins[65–69]. However, to evaluate ISF analytes in a noninvasive manner, these components must be extracted to the skin surface, which can be accomplished through reverse iontophoresis or sonophoresis. Using these methods, variations in the extraction efficiency and skin surface contamination can influence the accuracy, much as in sweat-based platforms. To address such issues, advanced sampling methodologies and refinement of each analyte monitoring approach is necessary.

Exercise-based wearable sweat biosensors. Early advances in epidermal wearable biosensing platforms focused on single analyte sensing with a wide range of targeted analytes (A.S.C., J.K., J.W. et al.)[1,29,49,50,66]. Such proof-of-concept demonstrations were made using new stress-resistant materials and sensor structures for achieving the high degree of skin conformability essential for reliable sweat sampling during exercise, such as tattoo-type platforms. Temporary tattoos, coupled with screen-printed flexible electrodes, offer an attractive platform for skin-worn biosensing devices as they allow direct and continuous contact with the skin surface (J.W. et al.)[50]. Such body-compliant sensors couple highly favorable substrate skin elasticity and tight contact with the skin with an attractive electrochemical performance. Tattoo-based epidermal biosensors have been shown to allow real-time, noninvasive measurements of key sweat electrolytes (pH, ammonium or sodium), heavy metals (Zn) and metabolites (lactate or ethanol) (J.K., J.W. et al.)[58,70–74]. For example, our group (J.W. et al.)[58] published the first demonstration, to our knowledge, of continuous monitoring of sweat lactate levels via epidermal electrochemical biosensors, providing a real-time profile of lactate sweat dynamics during exercise. Sweat lactate is a byproduct of local sweat gland metabolism, and intense physical activity induces higher generation rates. Although sweat lactate does not directly reflect the concurrent blood levels, it indicates the level of physical exertion experienced during prolonged exercise and can be used as a marker for athletic efficiency without invasive blood sampling. In the study in question[58], the human subject was asked to wear the printed temporary tattoo biosensor, modified with lactate oxidase for measuring sweat lactate during exercise. Sweat lactate indeed increased with higher exercise intensity.

A notable advance has been made in developing multiplexed sweat biosensor platforms for quantitative analysis of sweat based on a fully integrated patch-based wearable sensor array (Fig. 3a)[35]. Simultaneous noninvasive multianalyte sensing is extremely attractive but requires an accurate monitoring system. In this work, the Berkeley team demonstrated the simultaneous multiplexed detection of sweat metabolites (glucose and lactate) and electrolytes (sodium and potassium ions), along with skin temperature, by integrating a multisensing array. This pioneering work advanced the wearable sensing field by filling the gap between signal transduction, conditioning, data processing, wireless transmission and system integration, allowing in situ data processing and communication. This advance was accomplished by merging flexible patch-type sensors with a conformal circuit board for accurate assessment via advanced signal processing of the physiological states of the human subjects during prolonged exercise. Recently, multianalyte electrochemical sensing technology was demonstrated by weaving multiple sensing fibers into a soft fabric[75]. The glucose, Na^+, K^+ Ca^{2+} and pH sensing fibers, prepared by coating the recognition materials onto carbon nanotube fibers to form a coaxial structure, maintained their attractive real-time sensing performance under repeated deformations. Reliable in situ multianalyte monitoring is essential for greater personalized diagnostic and physiological monitoring capabilities in a single wearable device. Multianalyte sensing could also provide a measure of sweat rate for calibrating the target analyte signals toward improved physiological relevance. The reported system proved advantageous for monitoring fitness parameters during exercise, but its utility would be limited in continuous monitoring applications owing to its reliance on physical exertion for sweat generation.

In another example of the advantages of multiplexed wearable devices, notable advances were demonstrated through sweat glucose monitoring devices coupled with pH, humidity and temperature sensors and integrated with a transdermal drug delivery system (Fig. 3b)[40]. The sweat glucose biosensor was thus coupled with therapeutic applications toward the management of diabetes. The accurate measurement of physiologically relevant sweat glucose concentrations with epidermal biosensors faces several major challenges related to uncontrolled operational conditions (for example, varying temperature and pH), glucose contamination from various sources, irregular sampling rates and low sampling volumes.

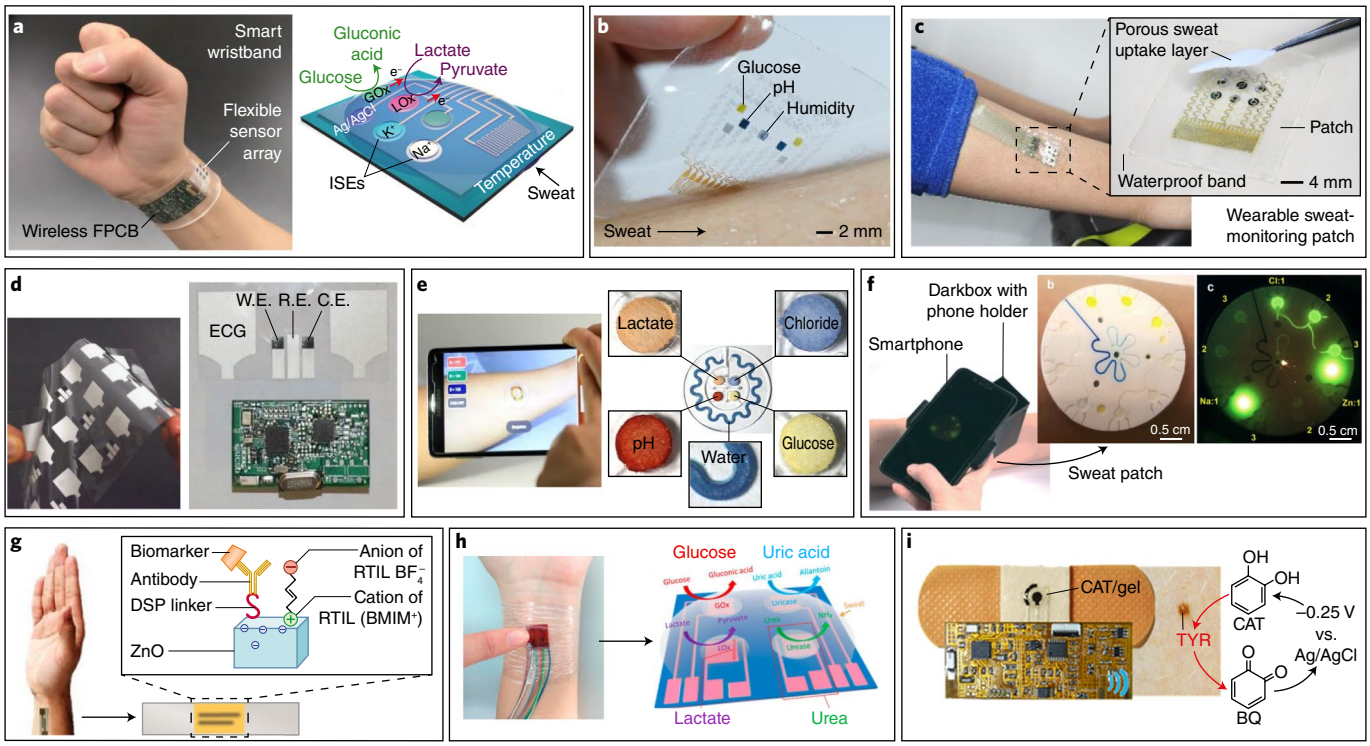

Fig. 3 | Epidermal biosensors for real-time monitoring of sweat chemistry. a, Integrated wearable sensor arrays for multiplexed perspiration analysis applied to wrist, with schematic representation of sensing array configuration. Fully integrated multianalyte sensor array for sweat-based monitoring of glucose, lactate, sodium, potassium and temperature during exercise, with wearable platform containing a sensing array as well as signal transduction, conditioning, processing and transmission components (adapted from ref. [35]). **b**, Graphene-based sweat sensor array for diabetes monitoring applied to human forearm. Multiplexed patch-type sensor array used for glucose monitoring during exercise, with simultaneous measurement of pH, temperature and humidity for glucose signal correction (adapted from ref. [40]). **c**, Wearable patch for sweat-based glucose monitoring and therapy applied to human forearm during exercise. Inset: sweat-based glucose monitoring sensor array configuration with porous sweat-uptake layer. Multiplexed patch is capable of operating in low sweat volumes (adapted from ref. [78]). **d**, Wearable chemical-electrophysiological hybrid biosensor configuration for real-time health and fitness monitoring, with example of screen-printed electrodes. Sensor provides simultaneous monitoring of sweat lactate levels and heart rate for athletic performance evaluation. W.E., R.E. and C.E. indicate working electrode, reference electrode and counter electrode, respectively (adapted from J.W. et al.[44]). **e**, Colorimetric microfluidic sweat sampling device configuration for chemical analysis of sweat, with representation of sweat-filled device and smartphone-based signal analysis. Device provides enhanced microfluidic sampling of sweat during exercise, with wireless measurement of target pH, lactate, glucose and chloride (adapted from ref. [34]). **f**, Fluorometric skin-interfaced microfluidic platform for the measurement of chloride, sodium and zinc in exercise-induced sweat. Fluorescent probes selectively react with target biomarkers upon sweat flow through the microfluidic system, with fluorescence intensity analyzed via smartphone-based imaging module, obviating the need for electrochemical or colorimetric analyses. CAT and BQ indicate catechol and benzoquinone, respectively (adapted from ref. [84]). **g**, Wearable diagnostic antibody-based biosensor detecting interleukin-6 and cortisol in human sweat using room temperature ionic liquids for enhanced antibody operational stability. Biosensor configuration using antibody immobilization is shown, with image of device applied to a human forearm. This device exhibits prolonged stability in pooled human sweat with continuous combinatorial analyte detection within the physiologically relevant concentration range (adapted from ref. [43]). **h**, Schematic representation of self-powered multifunctional electronic skin used for continuous monitoring of lactate, glucose, uric acid and urea in exercise-induced sweat using piezoelectric-linked enzymatic biosensors. During exercise, this device functions without an additional power supply through piezoelectric–enzymatic reaction coupling (adapted from ref. [56]). **i**, Wearable tyrosinase-sensing bandage for noninvasive melanoma biomarker screening. Inset: tyrosinase (TYR) detection (adapted from (J.W. et al.[86]).

Although several studies have indicated that sweat glucose concentrations can correlate with concurrent blood levels, these limitations can significantly impair the accuracy of collected data[64,76,77]. In an initial report, functionalized graphene was introduced to stretchable serpentine-structured electrodes for enhanced electrochemical biosensing of sweat glucose during physical exercise. The multiplexed sensing design allowed continuous correction of the measured results by addressing variations in the activity of the immobilized enzyme caused by pH, temperature and humidity fluctuations, with the goal of enhanced operational accuracy. However, sample contamination by external glucose sources (for example, glucose from the skin surface, environment or old samples) is yet to be accounted for. The developed platform was able to monitor fluctuations in human sweat glucose over a day and was further integrated into a closed-loop system using polymeric microneedles for delivering the drug metformin to regulate glucose in a mouse model. The successful combination of transdermal glucose detection with a drug delivery platform represents a significant advance toward reliable 'sense–act' systems. In further work, the system was improved for efficient sweat control and sensing accuracy by modifying the device assembly with multiple sweat-uptake and waterproof layers and by miniaturizing the sensor to enable reliable measurements using sweat volumes of ~1 μL (Fig. 3c)[78]. By overcoming sample volume limitations, these improvements targeted several other challenges of epidermal biosensors. However, efficient sample transport and reliable response would require a system that consistently provides fresh sample and accounts for fluctuations in the sweat rate.

The advances reported in these studies illustrate the potential of patch-type sweat biosensors for regulating glucose levels. Yet these devices require physical exercise for their operation and are thus not compatible with continuous glucose monitoring in daily life without exercise. Successful implementation of such sweat monitoring devices for managing diabetes would further require extensive large-scale population validation studies.

Our group (J.W. et al.)[44] has reported a new approach to multiplexed wearable sensing that fuses electrophysiological measurements with assays of biochemical markers. This method offers more comprehensive fitness monitoring by simultaneously measuring physiochemistry (sweat lactate) and electrophysiology (electrocardiogram) rather than requiring separate physical and chemical sensors. This idea was realized by developing a screen-printed hybrid chemical and physical patch-type sensor (Fig. 3d)[44]. On-body experiments involving a stationary cycle revealed that lactate and heart rate can be monitored simultaneously without cross-talk, representing an important first step toward multimodal wearable sensors for comprehensive understanding of human physiology. Such sensing platforms can provide enhanced monitoring of athlete performance during exercise but will require attention to potential variations in the sweat rate, applying multiplexed sensing of different parameters for fitness or healthcare monitoring application, similarly to previously discussed systems[35,40,41,78].

In addition to electrochemical detection techniques, colorimetric signal transduction has been exploited, taking advantage of its ability to monitor target analytes in sweat in connection to different indicator dyes[34,56,60,79–82]. Colorimetric analysis obviates the need to power the sensor platform, which can facilitate small and readily wearable devices, but requires additional read-out devices with data analysis for sensitive measurements, such as a camera with color analyzing software. Real-time optical monitoring of multiple sweat biomarkers can be accomplished using a colorimetric sensing system integrated with microfluidics for real-time sweat sampling. The developed device allows sophisticated sweat sampling and measurement based on a thin and soft closed microfluidic system that directly and rapidly collects the generated sweat without sweat evaporation or contamination, resolving the conventional challenges of sweat (Fig. 3e)[34]. Such skin-mounted fluidic devices have been designed to monitor multiple sweat biomarkers (for example, lactate, glucose, pH, chloride or sweat loss) through multiple channels and corresponding sensing reservoirs, along with quantification of sweat loss. The colorimetric data obtained with two human trials were analyzed and quantified through wireless data transmission. The Rogers group[83] further refined their epidermal, colorimetric sweat-sensing microfluidic platform via superabsorbent polymer valves that capture and store generated sweat for analysis of chloride concentrations with a goal of multiple sequential measurements. Our group (J.K., A.S.C., J.W. et al.)[38] has also recently developed an analogous skin-worn flexible sweat sampling microfluidic flow system with integrated electrochemical biosensing of lactate and glucose.

The latest advance in such microfluidic sweat monitoring technologies has been accomplished by incorporating fluorescent probes into a skin-interfaced system for accurate in situ measurement of chloride, sodium and zinc, with the resulting fluorescence evaluated via a smartphone-based imaging module (Fig. 3f)[84]. This optical-sensing fluidic approach offers sensitivity comparable to that of conventional laboratory techniques with operation in microliter volumes. Such expansion of viable signal generation and transduction methodologies is crucial for broadening the scope of targetable biomarkers, particularly when successfully coupled to biofluid sampling methods that do not necessitate exercise.

Several recent studies have also focused on the expansion of target biomarkers to include those related to hormone and immune responses. For instance, a wearable immunosensor for detecting cortisol and interleukin-6 in sweat has diagnostic potential (Fig. 3g)[43]. This platform was evaluated in vitro with human sweat, using room-temperature ionic liquids to compensate for variations in sweat pH while enhancing the stability of the antibody receptor for up to 96 h. Furthermore, label-free electrochemical impedance spectroscopy was applied to detect the analyte-binding event while porous polyamide membranes were used for effective sweat sampling in low volumes for application on the human finger or hand. Similarly, an alternative cortisol detection system has been reported that is based on MoS_2 nanosheets functionalized with cortisol antibodies[85]. Although such antibody-based bioassays hold great promise for expanding the scope of epidermal wearable biosensors, which focus primarily on enzymatic metabolite detection, their successful on-body use has yet to be demonstrated. Unlike epidermal enzyme-based biosensors, such immunosensors cannot be readily regenerated for continuous monitoring applications, and, along with other challenges of multistep affinity bioassays, these devices require further efforts and innovations.

Most recent progress in wearable biosensors has been made using electrochemical or optical methods, but piezoelectric biosensing systems have also been introduced as new electronic-skin platforms monitoring sweat metabolites (Fig. 3h)[56]. The resulting piezoelectric signal is driven by the body movement (during exercise) and depends on the analyte sweat concentration. This results in a self-powered biosensor capable of distinguishing sweat analyte concentrations and obviating the need for a power supply or battery. The validation of such proof-of-concept of wearable piezoelectric biosensors as self-powered device in real-world applications requires critical evaluation in terms of accuracy and duration of use.

Epidermal biosensors can also analyze the skin surface rather than detecting sweat or ISF biomarkers. Unlike earlier wearable biocatalytic sensors designed for detecting the corresponding metabolite substrates, a recently reported bandage-type biosensor proved capable of detecting the enzyme tyrosinase on the skin surface as an analyte (Fig. 3i; J.W. et al.[86]). This system represents, to our knowledge, the first example of a wearable device aimed at detecting an enzyme as a biomarker. Selective tyrosinase detection was accomplished by immobilizing catechol, the substrate of tyrosinase enzyme, on the sensor surface. The tyrosinase level was determined electrochemically by measuring the benzoquinone product of the enzymatic reaction. The attractive performance of this tyrosinase bandage biosensor shows promise for the rapid screening of melanoma. Bandage-type wearable sensors represent a rapidly emerging technology with considerable potential for low-cost decentralized (home or point-of-care) monitoring and diagnoses. Each system, however, still requires extensive on-body validation and human testing of clinical accuracy.

Iontophoresis-based epidermal biosensors. Epidermal biofluids (ISF and sweat) can also be noninvasively obtained through iontophoresis in important biomonitoring uses. This method involves the application of a mild current across the skin to induce ion migration between two skin-worn electrodes and can be accomplished at rest. Iontophoresis is a noninvasive method of transporting molecules through the skin without harming the skin surface or contacting blood. ISF can be extracted through reverse iontophoresis, which relies on application of a low current to induce a flux of positively charge ions toward the negatively charged skin surface and an electro-osmotic flow from anode to cathode. This flow further results in the movement of neutral molecules, such as glucose, toward the cathode. ISF glucose levels correlate well with blood glucose because ISF components diffuse directly from the capillary endothelium. The extracted glucose in ISF can be easily measured using glucose biosensors mounted on the skin. The first commercial demonstration of a reverse iontophoresis–based sensing platform was developed by Cygnus as a wearable, wrist-mounted system called the

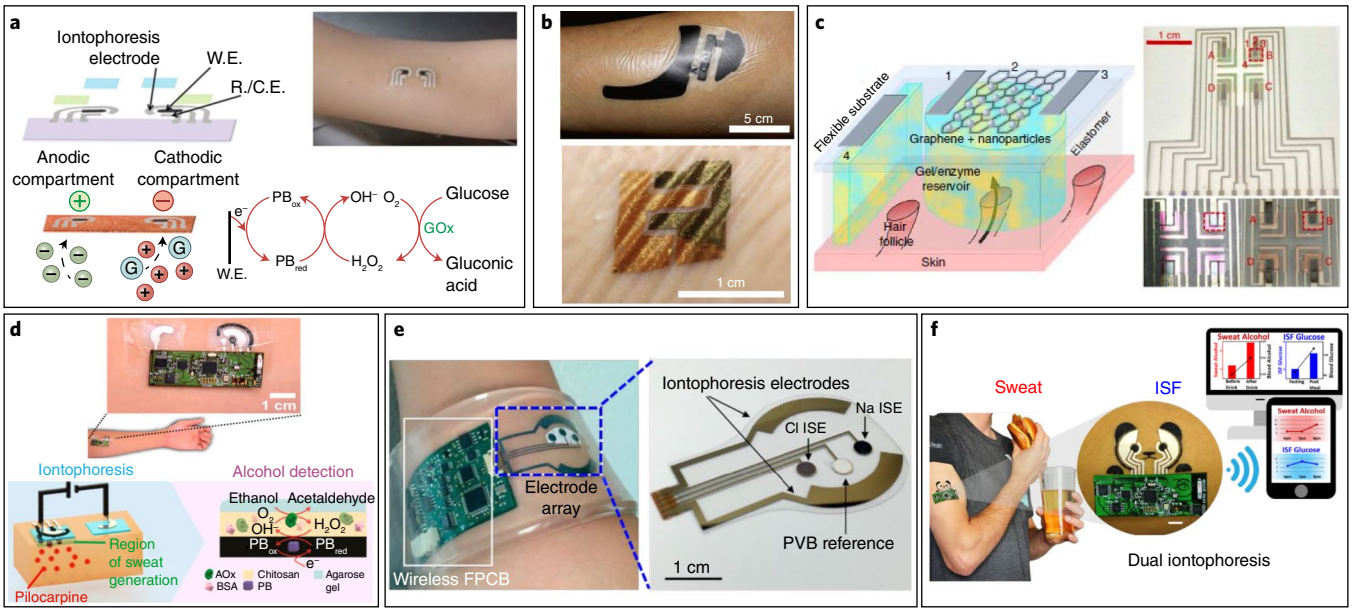

Fig. 4 | Epidermal iontophoretic biosensors. a, Epidermal reverse iontophoretic tattoo-based glucose sensor configuration and operation principle, with picture of device applied to a human subject. Proof-of-concept demonstration of reverse iontophoretic tattoo-based ISF glucose sensor. W.E. and R./C.E. indicate working electrode and reference/counter electrode, respectively (adapted from J.W. et al.[37]). **b**, Iontophoretic paper battery and skin-like biosensor for noninvasive blood glucose monitoring, applied to a human subject. Inclusion of hyaluronic acid facilitates enhanced ISF extraction for increased ISF glucose sampling reliability (adapted from ref. [87]). **c**, Transdermal, path-selective iontophoretic ISF sampling approach using miniaturized graphene-based pixel arrays for noninvasive glucose monitoring. Configuration of pixel-type biosensor array with four individual ISF extraction and detection locations. This proof-of-concept device, focusing on device architecture design rather than specific sensor implementation, can sample ISF through individual follicular pathways for enhanced glucose detection reliability over 6 h (adapted from ref. [88]). **d**, Epidermal iontophoretic alcohol-sensing tattoo applied to a human subject, with schematic representation of iontophoretic drug delivery and sensing principles. Device uses localized, drug-induced sweat generation for on-demand sampling (adapted from J.K., J.W. et al.[74]). **e**, Integrated wearable sensor array band for multiplexed sweat extraction and analysis applied to human wrist, with sensor array configuration. Devices provides simultaneous detection of chloride, sodium and glucose in iontophoretically induced sweat (adapted from ref. [41]). **f**, Device configuration and on-body application of simultaneous dual iontophoretic ISF and sweat sampling platform for the sampling and analysis of these two biofluids on a single platform without cross-contamination. This device can monitor sweat alcohol and ISF glucose simultaneously through the iontophoretic delivery of sweat-inducing pilocarpine and iontophoretic extraction of ISF glucose (adapted from J.K., A.S.C., J.W. et al.[93]).

GlucoWatch Biographer[30]. This US Food and Drug Administration (FDA)-approved device is capable of noninvasive glucose monitoring over a 12 h period with six measurements per hour. However, the GlucoWatch was withdrawn from the market in the early 2000s due to reported skin irritation caused by the reverse iontophoresis process, long warm-up period (2–3 h) and the necessity of calibration using an invasive blood glucose meter. This example indicates that commercialization of wearable biosensors requires careful evaluation in terms of accuracy and ease of use.

Later, work in our group (J.W. et al.)[37] resulted in the development of an iontophoresis-based platform using a body-compliant flexible tattoo platform through screen-printing of both the iontophoretic electrodes for reverse iontophoresis and the glucose biosensing electrodes (Fig. 4a). This integrated device addressed several limitations of the GlucoWatch: first, it minimized discomfort during reverse iontophoresis by reducing the applied iontophoresis current and glucose detection potential; second, it greatly reduced the price by relying on a disposable screen-printed tattoo platform; and third, it was easily mounted on the skin surface without hindrance to the wearer's movement. The performance of the tattoo sensors was evaluated in healthy human subjects by comparing the response obtained before and after meal and then validating the results with concurrent blood glucose test strips. This proof of concept highlighted the capability of disposable tattoo-based wearable glucose sensing platforms to use reverse iontophoresis for ISF sampling, but lacked electronics integration and validation of long-term operation toward continuous monitoring applications.

To enhance the collection of ISF glucose, the delivery of positively charged hyaluronic acid has been incorporated into wearable platforms, which leads to increased transport of glucose to the skin surface[87]. The extracted ISF glucose is measured by a conformal glucose oxidase (GOx)-based biosensor attached at the site of ISF extraction after the reverse iontophoresis process (Fig. 4b). This approach increases the ISF glucose sampling efficiency for more accurate sensing in relation to blood concentrations, indicating promise for enhanced noninvasive reverse iontophoresis–based monitoring applications that address the limitations of the GlucoWatch. These reverse iontophoresis–based glucose sensing devices take advantage of the close correlations between ISF and blood glucose levels, as well as the capability of reverse iontophoresis to sample ISF at rest. However, the efficiency of glucose extraction by reverse iontophoresis is difficult to control, which can lead to inconsistent volumes of sampled ISF and thus variations in glucose concentration.

Toward an end of greater consistency of reverse iontophoresis analyte extraction, a path-selective, graphene pixel–based glucose monitoring patch was recently developed (Fig. 4c)[88]. This platform applies an array of small 'pixels' designed to be roughly the size required to sample ISF from a single hair follicle, as the follicular path is the preferential, low resistance path of ISF extraction, and thus provide greater extraction reproducibility. Arrays of multiple pixels allow redundant measurements to be taken on a single platform for greater accuracy. Such reliable operation could prove crucial to the successful implementation of epidermal wearable biosensors. Successful on-body noninvasive glucose monitoring was

demonstrated for over 6 h. Extended operation is a major outstanding requirement for clinical translation and commercial viability.

Iontophoresis has also been widely used recently to stimulate local sweat secretion by loading the iontophoretic electrodes with a sweat stimulant (for example, pilocarpine and carbachol). Using this method, sweat generation can be controlled on demand, obviating the need for exercise and enabling measurement at rest. Iontophoresis was developed in 1959 by Gibson and Cooke[89], who introduced the use of the cationic drug pilocarpine for sweat generation. Pilocarpine can be delivered across the skin through charge repulsion at the anode compartment, leading to localized sweat production. This process was further developed as the commercial chloride ion monitoring product Macroduct by Wescor in pursuit of the FDA-approved diagnosis of cystic fibrosis[90,91]. A recent paper from our group (J.K., J.W. et al.)[75] describes the merger of an iontophoretic sweat-generation system with an amperometric biosensing system in a single wearable tattoo platform (Fig. 4d). This integrated tattoo biosensor measures sweat alcohol in the iontophoretically generated sweat within 10 min. Sweat alcohol represents a useful indicator for blood alcohol levels without time lag and the errors common to transdermal devices and breathalyzers. Highly selective alcohol measurements were achieved by coupling the alcohol oxidase enzymatic reaction with cathodic detection of the liberated peroxide product at the printed Prussian blue transducer. A wireless Bluetooth interface enabled signal transmission to a mobile device. The analytical performance was demonstrated and validated with healthy human subjects consuming different levels of a variety of alcoholic beverages. Iontophoresis-induced sweat generation obviates the need to exercise for sweat sampling. Yet, owing to potential variation in sweat rates, active calibration is required to ensure reliable measurement.

Other efforts have focused on integrating the iontophoretic sweat-generation compartment and sensing compartment on different skin mountable platforms. For example, using agonist delivery to generate sweat, a patch-type iontophoretic sweat sensor has been developed either for measuring sodium and chloride ions in cystic fibrosis diagnosis or for measuring glucose concentrations in healthy individuals (Fig. 4e)[41]. Specific sweat-generating profiles can be generated in response to stimulation with pilocarpine or alternative agonists, such as acetylcholine and methacholine. Device performance was evaluated by comparing electrolyte data from healthy subjects and those with cystic fibrosis; in addition, the ability of the sensor to detect glucose was assessed in the context of monitoring sugar consumption in healthy subjects. This advanced device was capable of noninvasively monitoring target biomarkers in a fully integrated platform with tailorable sweat generation profiles. However, the duration of sweat generation was limited to 60 min, with varying rates over that time, which could hinder continuous monitoring applications.

Future development of epidermal wearable biosensors should also expand their utility to the detection of various drugs to facilitate noninvasive pharmacokinetic studies. For example, a wearable sweat-based sensor has been developed to detect caffeine (a methylxanthine drug) using pilocarpine-based iontophoretic sweat stimulation or exercise-induced sweat[92]. Rather than using biological recognition, this sensing platform relies on direct anodic detection of caffeine at a carbon nanotube–based working electrode with a voltammetric scan. Although this device is not classified as a typical biosensor, the proof-of-principle experiments indicate the potential of such sensing systems for monitoring drugs and drug interactions in the human body, with the promise of theranostic (therapy plus diagnostic) applications farther into the future. Even so, the sensing device as described was not integrated with the sweat generation device, but rather coupled to a commercially available Macroduct sweat collector using pilocarpine delivery. For widespread pharmacokinetics studies performed at rest, a customized iontophoretic device should be integrated with the sensing platform. Additionally, a deeper understanding of blood–sweat drug concentration correlations will be required to facilitate meaningful data collection and interpretation.

Despite noteworthy advances in epidermal biosensors, the reported devices have been limited to analysis of a single biofluid. However, our group (J.K., A.S.C., J.W. et al.)[93] recently demonstrated the simultaneous sampling and analysis of two different epidermal biofluids with a single wearable platform through combined iontophoresis (Fig. 4f). This was accomplished by coupling sweat stimulation (via iontophoretic drug delivery) with ISF extraction (via reverse iontophoresis), enabling concurrent analysis of biomarkers in each biofluid. The system allows on-demand, controlled simultaneous sampling of two biofluids at physically separated locations on a single wearable tattoo platform. The biosensing performance has been demonstrated by measuring sweat alcohol and ISF glucose as model analytes in human subjects consuming food and alcoholic drink. For continued progress and before real-world use, next-generation noninvasive epidermal biosensing systems would require detailed studies of the correlations to blood levels.

Challenges and future prospects. The representative examples discussed in this section highlight the recent progress of epidermal wearable platforms for noninvasive monitoring in sweat or ISF and the future promise of such wearable epidermal biosensors. Substantial advances have been made recently in terms of device integration, sensing accuracy, sweat/ISF generation and replacement, signal transduction, data transmission and multiplexed sensing, along with related flexible and self-healing materials. Despite these advances, extensive efforts are still required to realize their full diagnostic potential, which should focus on the viability of extended use, critical correlation of sensor response to concurrent analyte blood concentrations, and efficient, controlled sampling of the target biofluids. Further attention is also needed to enhance sweat sampling and transport to improve detection reliability and relevance for monitoring dynamically changing concentrations. Multiplexed sensing platforms can further enhance the reliability of monitoring sweat analytes by correcting for variations in sweat flow, temperature, humidity and pH. The reported systems are particularly applicable in fitness monitoring, which fulfills the requirement of sweat generation through physical exercise. However, alternative sampling routes are required to increase the impact of epidermal devices for additional applications (for example, diabetes monitoring or alcohol monitoring). Moreover, noninvasive monitoring of new target biomarkers is desired to broaden the scope and impact of wearable biosensing systems.

Ocular wearable biosensors

Another biological fluid that can be exploited for monitoring physiological status is tears. Not only do biomarker molecules in tears diffuse directly from the blood and exhibit close tear–blood concentration correlations, but also tear analysis presents opportunities for the diagnosis of ocular disease. Tears are also less complex than blood and are part of the antifouling mechanism of the eye. These characteristics make human tears an attractive diagnostic biofluid for healthcare monitoring applications that can be sampled without blood contact[94–98].

Secretion and composition of tears. Human tears, or lachrymal fluid, are secreted by the lachrymal gland as a protecting film covering the eye. Tears contain both low- and high-molecular-weight compounds, such as protein, peptides, lipids, metabolites and electrolytes. In particular, tear glucose concentrations correlate well with blood glucose levels, reflecting the diffusion from the lachrymal artery when tears are sampled without any eye irritation or stimulation, which can compromise the relationship[94,95,99–101].

Despite the demonstrated correlations, sampling tears for in vitro diagnoses is associated with several errors that are due to the following: first, small sample volumes[102]; second, ease of evaporation during sample collection; third, variations in tear production among individuals and throughout the day[103]; and lastly, challenging collection methods that can affect the sampled analyte concentrations[104,105]. The accuracy of such in vitro tears diagnostic assays thus depends strongly on the collection method, with the most common strategies being via a glass capillary tube or the Schirmer's strip[106]. Reflex tears, generated during emotional or mechanical stimulation, have different compositions than basal tears, which make up the protective tear film covering the eye surface at all times. These variations and challenges highlight the need for developing wearable tears sensing platforms without eye irritation.

Tear-based wearable biosensors. Contact lens–based systems represent an attractive solution to tear collection issues as they can be worn without eye irritation and are in direct constant contact with basal tears[94,97,98]. These devices integrate all the necessary biosensing, data processing and power sources within the contact lens platform, which can lead to challenging design requirements. The rapid development of soft materials used for contact lens fabrication offers high degrees of flexibility to minimize eye irritation and avoid discomfort to the wearer. These materials also provide the oxygen permeability necessary to avoid oxygen deficiency and enhance the accuracy of continuous metabolite monitoring. Contact lens–based sensors were initially introduced using optical measurement of tear glucose based on the interaction of glucose with concanavalin A or phenylboronic acid derivatives[107,108].

The possibility of quantifying glucose in human tear fluid at physiological conditions using holographic contact lenses was also presented around the same time on the basis of advantages such as the ability to dispense with a battery, ease of reading, and continuous glucose signal monitoring[109]. Other contact lens–based optical sensors have involved the use of photonic crystal materials in combination with responsive hydrogels or fluorescent dyes for measuring glucose and other target analytes in tears[110–113]. The combination of such optical sensors with the use of smartphone-based microscopes, including algorithm-based applications, is expected to facilitate the readout of the biosensor response.

Further advances for the field came with the demonstration of electrochemical biosensing by the Parviz team[114–116]. This group investigated different biosensing strategies to achieve good sensitivity, linearity and accuracy. They were also able to resolve interference issues by introducing the dual sensor setup, which implements additional control (GOx-free) working and counter electrodes[114,115]. Further progress has since been made by embedding a wireless readout chip (2.4 GHz) and by powering the device with far-field electromagnetic radiation (3μW at a distance of 15 cm)[116].

As a result of these consistent endeavors, Google, in partnership with Novartis, made the most notable progress by applying their expertise in electronics miniaturization and applied medical technologies, respectively, toward development of a contact lens sensing platform for tear glucose monitoring[33]. The prototype consists of a wireless control chip, miniature electrochemical transducer and antenna on a soft contact lens platform with the glucose sensor embedded within a hydrogel matrix to noninvasively measure glucose in the surrounding tears (Fig. 5a). This industry partnership has been projected to accelerate the introduction of contact lens–based biosensors to the commercial market. However, there have been delays in the clinical trials and subsequent commercial release of this product, indicative of the technological challenges of successfully achieving a high-performing contact lens–based sensing platform.

Recently, 'smart' contact lenses for wireless ocular diagnostics have been further developed by combining glucose and ocular pressure contact lens sensors to integrate wireless in vivo glucose monitoring in the eye of a rabbit with in vitro monitoring of ocular pressure using a bovine eyeball (Fig. 5b)[117]. Although this device is capable of multiplexed sensing, the simultaneous operation of the two functionalities has not yet been demonstrated. Cross-talk and accuracy along with biocompatibility should be critically assessed in further studies with human subjects. The work was further expanded for integration of wireless power transfer circuits and displays on contact lens biosensors, visualizing the in vivo rabbit tear glucose response in real time (Fig. 5c)[118]. This advanced device focused on ensuring wearer comfort without hindrance to vision through the use of transparent, soft materials, while integrating wireless electronics to eliminate the need for an external power source. However, more studies are required to demonstrate sensing performance in vivo with human subjects and show viability of its use to measure variations in glucose throughout a day.

Another recent advance in wearable contact lens biosensors involved the use of smartphones for optical continuous glucose monitoring[112]. A hydrogel-based sensor with photonic microstructure was attached atop a commercial contact lens, and the reflective power was recorded using a smartphone in response to changes in tear glucose (Fig. 5d). This device offers fast and easy fabrication, along with a rapid and sensitive glucose response. Such capabilities present an attractive alternative to electrochemistry-based contact lens biosensors and address challenges of miniaturization in power transfer and data communication.

In addition to contact lens platforms, a small spring-like electrochemical sensor, consisting of multiple coiled wire electrodes coated with a protective polysaccharide-based hydrogel material, was designed by NovioSense for placement in the inferior conjunctival fornix to provide constant access to tear fluid (Fig. 5e). Such sensor placement at the base of the eye, behind the eyelid, provides continuous tear glucose measurements when coupled with wireless data transmission, without causing discomfort. A recent clinical trial demonstrated good correlation between tear and blood glucose concentrations in animals and humans, including those with type 1 diabetes[119].

Challenges and future prospects. Overall, tear-based sensors have focused primarily on glucose monitoring but show considerable promise for noninvasive sensing of other physiologically important biomarkers. The scope of new tear analytes can be expanded to additional metabolites and key electrolytes whose concentrations in tears display close relationships with those in blood. For example, direct tear-based noninvasive assays of catecholamines may improve the diagnosis of glaucoma[120]. As tear fluid contains thousands of proteins—the most abundant of which are lysozyme, lactoferrin and albumin—noninvasive tear monitoring could also be used to detect protein biomarkers correlated with disease[121]. Tear proteome analysis may be one approach for identifying such biomarkers linked with ocular disease. However, as with sweat, these applications require extensive validation of the tear–blood concentration correlation, as well as a validation of the relevance of a biomarker to ocular disease progression, along with a greater understanding of tear chemistry in general. A related challenge is to better understand the influence of the sampling procedure on tear composition.

Wearable contact lens tear monitoring platforms are advantageous because they do not cause any eye irritation and yield a relatively consistent tear fluid composition. Such systems have already proven attractive for monitoring health status and can be further expanded toward therapeutic applications with the potential enhancement of capabilities by miniaturization of the electronic interface and power source, with a goal of full integration onto the lens. Microfluidics could also be applied to challenges of tears sampling, such as small volume and ease of evaporation, to facilitate real-time, accurate tear monitoring. Such a fluidic platform

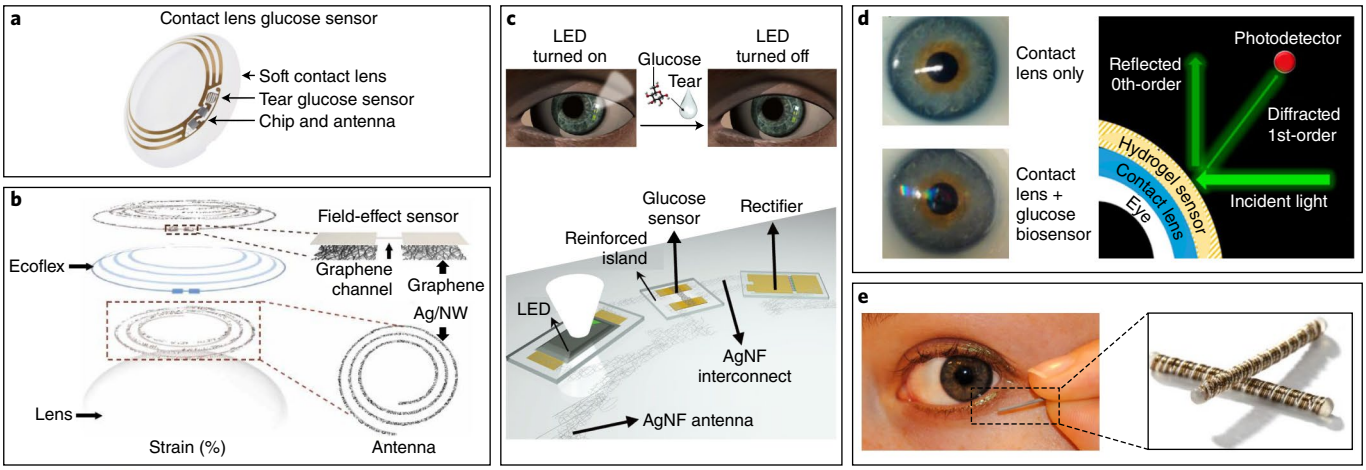

Fig. 5 | Tear-based biosensors. a, Contact lens sensor previously under development by Google and Novartis to measure tear glucose concentration in a miniaturized sensor. Prototype platform contained integrated electronics for sensor response processing and wireless transmission (adapted from https://sites.google.com/site/smartcontactlens/). **b**, Multifunctional wearable smart sensor system incorporated onto a contact lens for monitoring both glucose in tears and intraocular pressure using enzyme-functionalized graphene-silver nanowire hybrid nanostructures. The device proved capable of wirelessly detecting fluctuating glucose concentrations and pressure in a rabbit model in vivo and in a bovine eyeball in vitro (adapted from ref. [117]). **c**, A wireless glucose sensor incorporated into a contact lens platform with wireless power transfer circuitry and display pixels for a fully integrated and transparent platform that does not hinder vision. This device detects fluctuating tear glucose concentrations through a resistance-based enzymatic mechanism, which was demonstrated in a rabbit model (adapted from ref. [118]). **d**, Wearable contact lens tear glucose biosensor applied to an artificial eye, with schematic representation of smartphone-based quantification of glucose levels through reflection of incident light by the photonic microstructure within the lens. The smart contact lens system integrated with a glucose sensitive hydrogel monitors changing glucose concentrations in vitro without complicated fabrication procedures and allows rapid response time for continuous measurements (adapted from ref. [112]). **e**, NovioSense electrochemical tear glucose sensor. A small spring-like sensing device is designed to be placed within the conjunctival fornix for continuous access to tear glucose (adapted from http://noviosense.com).

was suggested by the Butt group[112] for integration with an optical monitoring system, but has not been demonstrated for biosensing applications. The successful realization of this idea would greatly enhance the accuracy of future tear biomonitoring.

Because of the sensitivity of the eye to foreign objects, in vivo evaluations of tear biosensors currently rely on animal studies, but further efforts and safety measures should lead to practical applications in human subjects. Compared with epidermally focused wearable biosensors, tear-based systems benefit from the advantage of continuous access to the target biofluid without the need for induction or extraction. However, difficult sampling procedures complicate reliable tear-based sensing platforms while contact lens–based systems suffer from design constraints imposed by the nature of their operating environment.

Oral-cavity wearable biosensors

The interest in saliva as a diagnostic fluid has advanced rapidly in recent years[122]. Many of the biomarkers in saliva pass directly from the bloodstream via transcellular or paracellular paths, making saliva the 'mirror of the human body' that reflects the body's physiological state to offer a noninvasive alternative to blood analysis. The high protein content of saliva makes it attractive for detecting disease and stress biomarkers in biomedical and fitness monitoring. Because saliva can be readily collected[123–125], it has been used in connection to in vitro diagnostic biosensors on strips or portable device platforms[126–134].

Secretion and composition of saliva. Saliva is a complex oral fluid that is produced mainly by the parotid gland and is composed of many constituents, including metabolites, enzymes, hormones, proteins, microorganisms and ions[125,135–140]. Several of these saliva biomarkers (for example, drug, hormones, metabolites or antibodies) have been used in clinical settings because they offer meaningful diagnostic information[140–144]. However, few studies have focused on developing wearable oral cavity biosensors, likely because of potential biofouling by the rich salivary protein content and the low concentrations of some target biomarkers. Despite these challenges, in-mouth biosensing platforms can offer an attractive, painless route for obtaining dynamic chemical information from saliva. Oral wearable platforms require the incorporation of biosensor and electronic interface into an orally mounted device, such as a mouthguard or denture-based system.

Saliva-based wearable biosensors. The first wearable oral sensor of which we are aware was demonstrated in the 1960s and was based on a partial denture platform for monitoring mastication, plaque pH and fluoride concentrations. However, such in-mouth operation required the replacement of several teeth by the sensors and was subject to risks associated with potential leakage of the internal sensor solution. The field of oral biosensing was expanded by Mannoor et al.[32], who reported graphene-based nanosensors printed onto water-soluble silk and transferred directly onto tooth enamel for passive, wireless detection of bacteria. These oral-cavity sensors were integrated with a resonant coil for battery-free operation and were capable of detecting salivary bacteria at the single cell level in vitro using a naturally occurring biorecognition element based on an antimicrobial peptide, along with label-free impedance transduction. This attractive wearable biosensing concept was targeted at remote monitoring of bacterial film development on the teeth and could be expanded to the extended monitoring of other salivary biomarkers.

The early demonstrations of oral-cavity sensor capabilities and potential, coupled with in vitro studies that showed good correlations between blood and salivary metabolite levels, encouraged recent research toward the development of modern oral-cavity salivary metabolite sensors, particularly in connection to wearable mouthguard platforms. Our group (J.K., J.W. et al.)[145] developed mouthguard-based salivary metabolite electrochemical biosensors through integration of screen-printed enzymatic electrodes.

Salivary lactate correlates well with blood lactate and could be used to assess physical stress and performance[146,147]. This device is capable of selectively detecting salivary lactate electrochemically using the lactate oxidase enzyme; protection against biofouling in undiluted human salivary samples is conferred by electropolymerized *o*-phenylenediamine for continuous, noninvasive physiological monitoring of an individual's fitness state.

We (J.K., J.W. et al.)[36] have further continued development of oral-cavity sensors by demonstrating a mouthguard-based uric acid biosensor that incorporates anatomically miniaturized instrumentation electronics featuring a potentiostat, a microcontroller, and a Bluetooth low energy (BLE) transceiver for monitoring salivary uric acid levels with an eye toward clinical applications (Fig. 6a). This platform enables noninvasive monitoring of salivary uric acid as a proxy for blood uric acid, which is a biomarker for various diseases (for example, hyperuricemia, gout and renal syndrome), and it displays sensitive, selective, stable and rapid response, enabling us to obtain dynamic chemical data on salivary biomarkers in the oral cavity. Although these mouthguard-based biosensing devices are well suited for fitness or diagnostic applications, more discrete platforms would be required for extended use, such as for continuous glucose monitoring in daily life.

Oral biosensing devices have been further miniaturized to a detachable 'cavitas sensor' device to measure salivary glucose on a mouthguard platform fabricated to fit over the wearer's teeth (Fig. 6b)[148]. The sensors are based on a GO_X-modified poly(ethylene terephthalate) glycol surface, and the device is seamlessly integrated with a wireless transmitter on a custom-fitted monolithic mouthguard. This configuration enables the telemetric measurement of salivary glucose in artificial saliva over the relevant physiological range (5–1,000 μM), and the device has been further characterized through connection to a phantom jaw, which mimics the human oral cavity, with a saliva flow system.

The correlation between blood and salivary glucose reflects the diffusion and active transport of blood components to the salivary gland[144], providing a highly advantageous, easily accessible route for glucose sampling. In the case of diabetes, changes in hormonal and neural balance may affect the salivary glands, which act as a filter from the blood, and lead to increased secretion of salivary glucose. Salivary glucose can thus offer an alternative, painless screening route for patients with diabetes[149–154]. Soni et al.[126] found the correlation between blood and saliva glucose concentrations to be $R = 0.64$ in healthy subjects, whereas those with diabetes show a much closer relationship, with $R = 0.95$. However, further large-population studies are required before considering the use of salivary glucose for screening or monitoring diabetes in integration with a wearable, miniaturized platform.

Another wearable sensor based on an oral-cavity platform recently has been demonstrated in in-mouth operation with a human subject (Fig. 6c)[155]. Such oral sensing was realized by introducing biocompatible materials, such as porous silk and hydrogels, on a tooth-mounted oral cavity sensor capable of wireless monitoring of foods during ingestion. The sensor measured fluid properties such as alcohol content, salinity, sugars, pH and temperature in vivo using RF sensors. However, bringing this strategy to practical real-life applications would require critical evaluation of the selectivity toward the target analytes to ensure accuracy.

An alternative in vivo oral monitoring device has also been developed for sodium intake via long-range wireless telemetry (Fig. 6d)[156]. This oral sensing platform relies on a user-comfortable system using ultrathin stretchable electronics along with miniaturized sensors. The device has been demonstrated in human subjects, proving its feasibility for real-time monitoring of sodium consumption, which is desired for managing hypertension. However, toxicity of the device was evaluated without the chemical sensing layer, and hence practical oral-cavity applications would require further critical assessment along with a biocompatible recognition layer. Further efforts are also needed for measuring sodium uptake during food and drink consumption. Overall, the recently developed in-mouth sensing platforms require additional critical evaluations to ensure the safety and reliability necessary for future deployment of such systems. Particular attention should be given to minimizing surface fouling and contamination caused by other saliva constituents and food debris, respectively, and to ensuring the safety of these devices.

Challenges and future prospects. Despite the promise of saliva as a noninvasive diagnostic fluid, challenges remain regarding the realization of widespread, accurate oral monitoring applications. The concentrations of many important biomarkers in saliva are substantially lower than in blood, requiring highly sensitive sensors for accurate monitoring. Compared with other noninvasively sampled biofluids, saliva can be readily sampled without complicated procedures, but it is composed of a rich matrix of constituents that can also be easily contaminated by external factors (for example, food and drink). Caution must also be used to avoid potential gum bleeding, which would lead to contamination or false signals. The high concentrations of protein in saliva, including mucins and proteolytic enzymes, along with food debris, can lead to rapid biofouling of the oral cavity sensor through nonspecific adsorption at the transducer surface. Such challenges can be addressed by developing permselective protective sensor coatings that exclude macromolecules from the surface.

Future work toward practical in-mouth applications requires detailed validation studies in comparison with blood and critical assessment of safety issues, such as biocompatibility, potential toxicity, sterilization and operational stability for in-mouth operation. Effective device encapsulation (including the supporting electronic interface and power supply) and use of biocompatible materials are essential for eliminating risks related to their contact with the saliva (in particular, chemical leaching to the surrounding fluid). Such encapsulation is also essential for protecting the functionality of the electronics. Continuous discovery of new saliva biomarkers will further be helpful for expanding the diagnostic scope of saliva. Such diagnostic capabilities can benefit from the introduction of multiplexed oral cavity biosensors.

Discussion

In this review, we have highlighted the most prominent approaches and the latest progress involving representative examples of modern wearable biosensors. A plethora of innovative wearable biosensing devices have already been demonstrated in diverse applications, ranging from the detection of metabolites (for example, lactate or glucose) to the monitoring of electrolytes (for example, sodium, potassium or calcium) in fluids such as sweat, ISF, saliva or tears in connection to enzymatic and ion-recognition reactions. These demonstrations have shown that wearable biosensors have immense potential for real-world applications. Such progress has benefited from the refinement of multiplexed sensing platforms, improved biofluid sampling and advances in flexible materials and wireless electronics. These advances have greatly enhanced the reliability of wearable biosensor, the analyte monitoring capabilities and wearability.

Despite tremendous recent progress in wearable biosensors, the state of the art in this field remains at demonstrating proof-of-concept wearable biosensing platforms for detecting several representative biomarkers, and only small steps can be taken toward practical applications in the field. Wearable biosensors face many fundamental challenges and technological gaps related to the scope, validation, stability and accuracy, along with power (Box 1)[1,42,157–167], communication (Box 2)[1,168] and security and privacy (Box 3)[1,169–172] issues. Overcoming such technological challenges is critical to the successful growth of wearable biosensors toward widespread

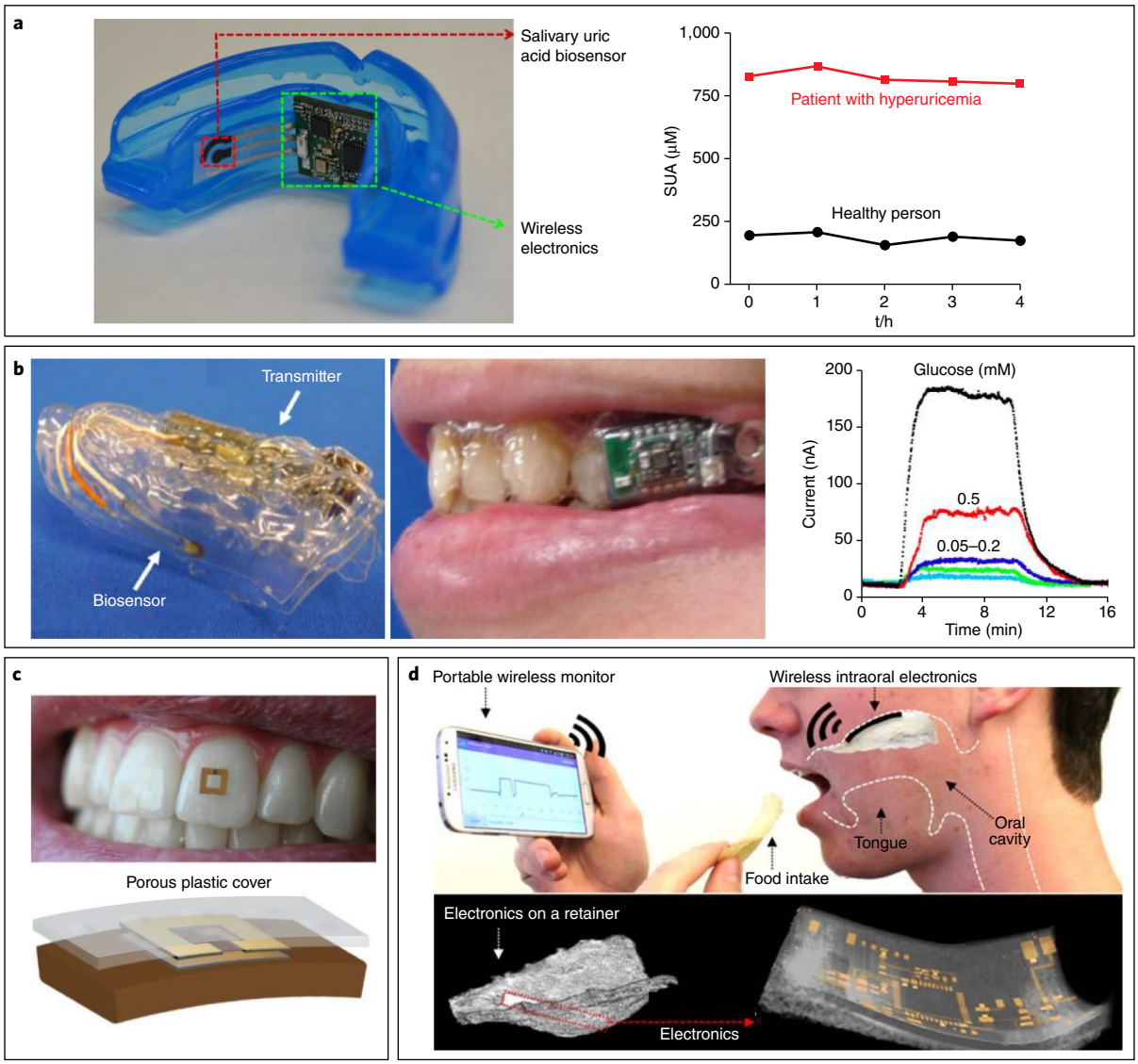

Fig. 6 | Saliva-based biosensors. a, Mouthguard-based wearable salivary uric acid biosensing platform with integrated wireless electronics and analysis of salivary uric acid concentrations in a healthy volunteer and a subject with hyperuricemia. This platform exhibited selective uric acid detection in undiluted human saliva to monitor the response or uric acid levels of a patient with hyperuricemia during treatment (adapted from J.K., J.W. et al.[36]). **b**, Mouthguard-based sensor for glucose monitoring in saliva with on-body application and analysis of increasing glucose concentrations. Fully integrated saliva glucose sensor aims toward continuous in-mouth glucose monitoring (adapted from refs. [97,148]). **c**, On-body depiction and cross-sectional configuration of radio frequency trilayer tooth-mounted sensor for wireless monitoring of food consumption. This dielectric sensor fabricated with biocompatible materials is capable of being mounted onto tooth enamel to detect foods and fluids during ingestion when functionalized with analyte-sensitive layers. Projected uses were for detection of sugars, alcohol, salinity, pH and temperature (adapted from ref. [155]). **d**, Operational principles and electronics configuration of a wireless, user-comfortable sensing platform for long-range oral monitoring of sodium intake during hypertension management. Electrochemical sodium sensing was demonstrated in vitro as well as in vivo with the orally mounted, biocompatible sensing platform (adapted from ref. [156]).

commercial realization. Some of these challenges are specific to the individual platforms or target analytes whereas others are shared by all wearable biosensing systems.

Toward measurement of a wider range of biomarkers. Most current wearable biosensing devices measure a small number of biomarkers. Going forward, greater efforts should focus on new biosensor formats and improved knowledge of noninvasively sampled biofluids to monitor a wider range of biomarkers. Understanding the composition of each biofluid and its relation to blood chemistry and to certain medical disorders will be essential to expand the reach of wearable technology in the healthcare arena, as well as to the widespread acceptance of these devices by the clinical community. The real-time correlation of analyte levels in noninvasive biofluids to concurrent blood concentrations is crucial to such acceptance. Rigorous and reproducible interpretation of biosensor readings in the real world is also an ongoing goal, particularly in applications where clinical or actionable responses may be required.

Going forward, a systematic, in-depth analysis of the composition of each of the different biofluids will be vital for identifying new biomarkers (for example, metabolites, proteins and nucleic acids) that previously have remained out of the scope of wearable sensors. Moreover, the evaluation of their dynamic concentration fluctuations under different scenarios may also provide new insights into circadian rhythms, disease trajectories and wellness over time. Noninvasive sensing may also be expanded beyond the measurement

Box 1 | Wearable biosensor power challenges

Wearable biosensors can be powered through a variety of means[1,42,157–167]. Most wearable biosensor power consumption arises from three main sources: first, powering of the sensors detecting the biomarkers (with a concomitant increase in power consumption as sensing is increasingly multiplexed); second, data processing, which involves a trade-off between energy consumption and data collection rate; and finally, wireless communication (both communication with other integrated sensors and data transmission). Meeting these power needs successfully requires multiple approaches[180–190]. These include safe high-energy wearable batteries, alternative energy harvesting and storage devices (for example, biofuel cell, solar cell, thermoelectric, piezoelectric, triboelectric, supercapacitor, or a combination of sources), wireless energy transfer, energy-efficient sensing devices, and self-powered biosensors based on biofuel cells using the analyte as the fuel. Furthermore, controlling and adjusting the sampling frequency and data transmission on the basis of the desired information and wearer activity could increase efficiency. For example, storing information while the device is asleep without communicating to the end user greatly reduces power consumption from data transmission.

Box 2 | Wearable biosensor communication challenges

To realize their full potential, wearable biosensors must be capable of wireless communication among individual wearers, multiplexed biosensors, and computing devices[1,168]. They must also be capable of long-distance data transmission and achieve these goals in an energy-efficient manner.

When assessing a communication protocol for a device, several criteria are taken into account: device power consumption, amount of data generated. required bandwidth, and compatibility with sensor circuitry. Strategies for wireless communication include the following (J.K. and J.W.)[191]: first, Bluetooth—or, more commonly, Bluetooth low energy (BLE)—which consumes less power, but also has the limitation of a 100-m distance limit for reception; and second, near field communication RFID (radio frequency identification), which is battery-free, but requires close proximity for signal reception.

Periodic data transmission depending on the desired biochemical information and energy requirements is one approach being explored to address the communication constraints of current devices. Another is the development of radical wireless technologies for long-distance data transmission within a high-density network of wearable devices.

of a few limited metabolites and electrolytes, as currently practiced, to a situation in which a whole slew of protein disease markers, hormones and stress markers are assessed using noninvasive immunoassays. Similarly, further opportunities may open up in exploring new types of bodily fluid (beyond ISF, sweat, tears and saliva), such as urine, mucus and semen. Such real-time analysis of a wider range of biomarkers in a wider range of biofluids would ultimately benefit other areas of biomedicine, such as biomarker-directed clinical development of new experimental therapies.

New wearable immunosensors will require advanced microfluidic platforms, carrying multiple steps (for example, tagging, washing and receptor regeneration common to bioaffinity assays), along with long reaction times for detecting very low biomarker concentrations. Such on-body bioaffinity assays could be simplified using label-free detection schemes[173,174]. Future wearable immunosensors hold considerable promise not only for healthcare and fitness applications but also for a variety of biodefense applications.

The integration of multianalyte sensing will be essential to the future adoption of wearable biosensors for tracking wearer health at the molecular level. Although most early wearable devices have focused primarily on single measurements, efforts should continue toward the simultaneous noninvasive monitoring of a wide panel of biomarkers. This more comprehensive analysis can give not only a broader analysis of the physiological state, but also provide for active calibration and correction of the response for more accurate monitoring. Furthermore, incorporation of multiple sensing approaches for the same analyte could lead to improved biosensor reliability. Efforts should also continue to emphasize the development of multimodal wearable sensors that fuse chemical, electrophysiological and physical sensors. The combination of different wearable sensor modalities should lead to a more comprehensive monitoring of human physiology and could find widespread applications, ranging from monitoring neonates to the monitoring of the elderly.

Although access and real-time analysis of noninvasively sampled biofluids promises new and rich diagnostics information, successful realization of wearable biosensors in healthcare will require extensive validation and large-scale correlation studies with gold-standard blood-based clinical assays. These rigorous large population studies—and the correlation of wearable sensor data with data from blood assays—will be requisite for developing reliable and safe wearable biosensing diagnostic platforms and will likely necessitate further connection to large-scale medical data mining, the Internet of Things, cloud computing and machine learning methods to take full advantage of the data in the context of healthcare settings.

Accuracy and stability. Ensuring that wearable sensor responses are both accurate and reliable will be critical to their acceptance in the marketplace. Accuracy is often compromised by surface fouling effects, which represent a major challenge to the continuous operation of on-body biosensors. During such applications, repetitive measurements are carried out over an extended period of time. To ensure the reliability of the response during prolonged on-body operation, robust antifouling surface protection is desired along with active calibration mechanisms (for example, multimodal, multianalyte sensing and drift correction). Biofouling is driven by the accumulation of proteins, cells or macromolecules on the sensor surface through nonspecific binding. Such rapid adsorption impedes the diffusion of the target analyte to the sensor surface, leading to a gradual decrease of the sensing signal over the time. Fouling of the surface of wearable biosensors, particularly those operating in sweat or tears over short durations, is expected to be less severe compared with that observed with implantable or minimally invasive sensors. In contrast, substantial biofouling is expected for saliva-based oral-cavity biosensors, as the complex saliva matrix contains a much higher protein content than noninvasive biofluids such as sweat or tears. Such oral-cavity biosensors would thus require special attention to the surface protective coatings. The sensor coating materials should be carefully selected to minimize biofouling effects and exclude coexisting electroactive interference while retaining enzyme at the sensor surface and avoiding leakage of potentially toxic sensor components.

Unlike traditional (laboratory-based) biosensors, wearable biosensors can be exposed to harsh and fluctuating conditions (for example, temperature) during prolonged outdoor activity in uncontrolled environments. Such severe conditions may affect the stability of their fragile bioreceptors. Multiplexed sensing, including both biosensors and physical sensors, could provide active calibration for variations in temperature, pH and humidity.

Achieving wearable biosensors with long-term operational and storage stability requires a proper attention to the receptor

Box 3 | Data security in wearable biosensors

With the advent of wearable biosensors comes new security risks[1,169–172]. A key benefit of using wearable biosensors for healthcare applications is the ability to monitor patients' health status in real time, remotely and continuously. Yet these advanced capabilities could cause users harm if the hardware and software systems are not designed with security and privacy in mind. Access to individuals' biomedical data should be strictly limited to authorized user to avoid compromising privacy. Further, collected biomarker metrics that lead to actionable interventions (such as drug delivery) could have life-threatening or serious health consequences. While comprehensive protection of collected data is critical for a reliable, safe operation, such data protection is challenging considering the goal of seamless connectivity and wireless data transmission. The network connected to a user's sensor data has a significant potential risk of outsider and insider security attacks. The threat of an outsider attack can be mitigated by reliable authentication and encryption techniques. Data security risks become more severe in cases of an insider attack by those possessing legitimate access to raw data. For example, the attacker can add false health data that may influence a patient's diagnosis and treatment. Early detection of such intrusion will minimize security risks and will ensure the confidentiality, dependability and integrity of healthcare data generated by wearable biosensors.

Quite apart from these security issues, the high data volume arising from continuous real-time measurements using wearable biosensors requires the implementation of intelligent data processing protocols (J.W. et al.)[1]. Some approaches that are commonly applied to data derived from wearables include data cleaning and filtering processes (for example, noise filtration), which can reduce wireless data transfer rates and energy consumption. Furthermore, expanded data mining protocols can predict potentially dangerous situations and establish correlations between sensor signal and clinical diagnostics among a large population of wearers.

immobilization, surface chemistry and storage conditions. Accurate on-body measurements also require attention to potential contamination from the surroundings, carryover from mixing with old fluid, and continuous signal drift (and related sensor calibration). These issues can be partially addressed using proper microfluidic sampling systems and optimizing surface coating techniques.

System integration and hardware. In addition to challenges stemming from biosensing components, the integration of effective hardware is essential for overall device operation and for the successful realization of these wearable platforms. Although not limited to wearable biosensors, attention to hardware, power and communication issues is crucial for the practical utility of these sensing devices. The hardware components must have a high level of integration with the biosensor platform and have varied requirements depending on the specific application. A wireless electronic printed circuit board containing a fully functional microcontroller is a widely used platform for wireless electronics because of its flexibility and cost-effectiveness. The printed circuit board can be further integrated with a battery (the most commonly used power source) by encapsulation in biocompatible insulating materials (for example, parylene-C) for safety. Another key requirement for wearable devices is maintaining low power consumption during continuous, prolonged monitoring while providing the wearer (and other end users) with useful, timely chemical information. This may require a trade-off between energy consumption and data rate, particularly when high sampling frequency is required. Efficient data processing and effective and safe communication of the collected data are also extremely important requirements.

New data mining algorithms are being developed to make sense of the large amount of data and predict patterns in connection to specific applications. The careful interpretation of collected data and thorough verification of the biosensor response is vital for wearable devices that monitor conditions used for follow-up clinical action, by the wearer or autonomously via a closed-loop system (for example, glucose monitoring leading to insulin delivery).

The provision of power to wearable biosensing platforms (see Box 1) can be accomplished in several ways, with the most common approach being lithium ion or alkaline batteries. These devices exhibit long lifetimes for extended biosensor operation; however, they are bulky and can pose toxicity issues, particularly with lithium ion–based systems[175,176]. Alternatively, batteries have been developed on stretchable and flexible materials for greater wearability, but have not yet demonstrated sufficient energy density for long-term use[177–179].

Major advances have been made in wearable supercapacitor technology as well. These materials have shown fast charge and discharge capacity, but also possess low gravimetric and volumetric energy densities[180–182]. Wearable power sources have also been reported that harvest energy during operation, depending on the type of wearable platform being powered. Energy can be harvested from light with wearable solar cells[183,184], motion with piezoelectric or triboelectric devices[185,186], heat with thermoelectric materials[187,188], or chemical constituents of the sampled biofluids with wearable biofuel cells[189–192]. Wearable biofuel cells, in particular, are a promising way to power noninvasive wearable platforms as they harvest energy from the same biofluids of interest and can operate as self-powered biosensors, but they still suffer from the stability issues discussed above[42,193,194].

One way of maximizing benefits is to combine several of the above approaches. For instance, a wearable supercapacitor might be implemented to store energy harvested using a wearable biofuel cell when the energy is not immediately needed. Advances in wearable power sources are a significant need, particularly with increases in energy demands caused by multiplexed sensing platforms. Researchers have focused on a combination approaches that involve the development of both the power sources and the design of more energy-efficient devices and adaptive algorithms to decrease energy demands. Such research has been extensively discussed elsewhere (J.W. et al.)[1].

Translation to the commercial market. The global wearable sensors market was valued at roughly $150 million in 2016 and is projected to reach $2.86 billion by 2025, according to a recent market report (https://www.grandviewresearch.com/industry-analysis/global-wearable-sensor-market). A large portion of this future market share is expected to be made up of wearable biosensors, primarily for noninvasive glucose monitoring[2]. The slower than anticipated rate of introduction of noninvasive biosensing platforms to the commercial market has depressed market expectation; however, with the rapid growth of research reports and proof-of-concept demonstrations, many are still bullish about the market prospects of wearable biosensors.

The successful translation of wearable biosensors and proof-of-concept demonstrations to the commercial market faces several hurdles related to their fundamental operation. For completely reliable use, wearable devices must overcome stability issues caused by prolonged operation under uncontrolled conditions, biofouling from constituents present in the sampled biofluids, and intrinsic instabilities of the biological recognition components themselves. Furthermore, the devices must be capable of robust operation without the need for constant recalibration (common in laboratory settings). The sensor preparation thus must ensure high bioreceptor stability to maintain accuracy and reliability of the response. Also, a

proper fluid sampling system, such as microfluidics, is desirable to provide effective and rapid transport of the biofluid over the sensor and ensure a reproducible and accurate signal, along with negligible sample contamination and carryover. Such advanced wearable fluidic systems could also facilitate multistep bioaffinity assays, particularly for immunoassays.

The regeneration of immunosensors is another major challenge to overcome if prolonged use of wearables is to be attained. Fully integrated wearable biosensing platforms would require incorporation of wireless electronics (integrated with an energy source) to facilitate the data processing and secure signal transmission. Furthermore, the use of mobile devices and smartphone-based microscopes, including algorithm-based applications, is expected to facilitate the readout of the response in optical wearable biosensors[112,113,195]. Considering all the above challenges, we are only at the beginning of understanding how wearable biosensor technologies can improve our health and performance.

Outlook. Wearable biosensors are expected to become more streamlined, moving away from the wrist and into textiles and fashion accessories that blend into a wearer's daily life. Some of these devices will require disposable components to address fouling issues. Future wearable biosensors will noninvasively monitor a wide range of biomarkers (including proteins and nucleic acids), ultimately enabling a comprehensive medical diagnostics and performance assessment. The acceptance of these noninvasive biosensors by the medical community will require extensive and successful validation in human testing and improved understanding of the clinical relevancy of sensor information. Given the competitive research and tremendous commercial opportunities in wearable biosensors, we anticipate exciting new developments in the near future. The wearable sensors market is thus expected to continue its rapid growth and continue its trajectory to changing and improving people lives.

Received: 16 February 2018; Accepted: 19 November 2018;
Published online: 25 February 2019

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Acknowledgements

This work was supported by the Defense Threat Reduction Agency Joint Science and Technology Office for Chemical and Biological Defense (HDTRA 1-16-1-0013). A.S.C. acknowledges funding through NIH NIAAA T32 Training Grant AA013525.

Competing interests

The authors declare no competing financial interests.

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